

Serial No. 09/156,367

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Examiner: Marianne P. Allen

claimed. Support for these claim amendments can be found throughout the specification, *e.g.*, at page 3, line 23 through page 4, line 2.

Claims 1 and 14 have been amended to clarify that the activated MLK activity is an enzymatic activity, an ability to bind the SEK1 protein, or an ability to phosphorylate the SEK1 protein. Claim 19 has also been amended to similarly clarify that MLK activity of cell-free MLK is an enzymatic activity, an ability to bind the SEK1 protein, or an ability to phosphorylate the SEK1 protein. Support for these amendments can be found in the specification at, *e.g.*, page 9, lines 8-10; and at page 12, lines 23-25.

Claims 2 and 9 have been amended to clarify that the cells express the mutated protein. Support for these claim amendments can be found at page 14, lines 12-5.

Claim 17 has been amended to clarify that the surviving neuronal cells are transfected with nucleic acid encoding the mutated protein. Support for this claim amendment can be found at page 4, lines 23-25.

Claim 14 has been amended to correct the claim language, adopting "compound" (which is used in step (b)), and dropping "MLK inhibitor". Applicants regret this obvious typographical error.

Claim 16 has been amended to correct a regretted typographical error.

Claims 19 and 24 have been amended to clarify that the MLK protein is MLK1, MLK2, MLK3, or a combination thereof. Support for these amendments can be found throughout the specification, particularly in claims 20 and 24 as originally filed.

Claim 19 has also been amended to clarify the steps of the claimed method. Support for this claim amendment can be found throughout the specification, particularly at page 4, lines 7-16; and at page 14, lines 19 through page 18, line 7.

Claim 21 has been amended to change the antecedent basis to a pending claim. Claim 21 has also been amended to clarify that the enzymatic activity is a kinase activity. Support for this claim amendment can be found throughout the specification, for example, at page 9, lines 11-14; and at page 4, lines 10-11.

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Claim 30 has been amended to clarify that the viability step is for determining whether the compound has an ability to prevent neuronal cell death. Support for this claim amendment can be found in the specification, for example, at page 14, lines 3-10.

Claims 7, 8, 12, 13, 22, and 23 have been amended to correct the antecedent basis for these claims to depend upon new claim 46 (claims 7 and 8), new claim 47 (claims 12 and 13) new claim 51 (claims 22 and 23)

Claim 45 has been added to claim a method for detecting a compound that can both inhibit MLK activity and prevent neuronal cell death. Support for this new claim can be found in claim 19 as originally filed.

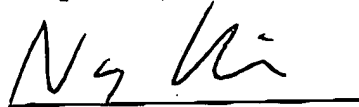
The above amendments of the claims are done without prejudice to further prosecution of other embodiments of this invention in a continuation, continuation-in-part, divisional, or other related application. None of the above amendments adds any new matter to the Application.

CONCLUSION

Applicant submit that the present amendments place the claims in better condition for allowance. If the Examiner believes that any further discussion of this communication would be helpful, she is encouraged to contact the undersigned by telephone.

No fees are believed to be due in connection with this communication. However, please apply any additional charges, or credit any overpayment, to our Deposit Account No. 08-0219.

Respectfully submitted,



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APPENDIX A

Marked-up Version of the Amended Claims Pursuant to 37 C.F.R. §1.121(c)(1)(ii)

1. (Thrice Amended) A method for assessing a compound's ability to prevent neuronal cell death [occurring in a mammal susceptible to or having a neurological condition], comprising:

a) contacting a compound with cultured neuronal cells having activated MLK activity, wherein the activated MLK activity is selected from the group consisting of an enzymatic activity, an ability to bind a SEK1 protein, and an ability to phosphorylate a SEK1 protein;

b) determining the number of cultured neuronal cells that die;
wherein a decreased number of dead cultured neuronal cells in the presence of the compound compared to the number of dead cultured neuronal cells in the absence of the compound is indicative of the compound's ability to prevent neuronal cell death [occurring in a mammal susceptible to or having a neurological condition].

2. (Once Amended) The method of Claim 1, wherein the neuronal cells are [transfected with] expressing a mutated protein or treated with a neurotoxin to induce apoptosis.

7. (Once Amended) The [method] compound of Claim [1] 46, wherein the neurological condition is a neurological disease whereby glutamate or kainic acid mediated excitotoxicity is involved in neuronal cell death.

8. (Once Amended) The [method] compound of Claim [1] 46, wherein the neurological condition is Huntington's disease or Alzheimer's disease.

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9. (Twice Amended) A method for assessing a compound's ability to prevent neuronal cell death [occurring in a mammal susceptible to or having a neurological condition], comprising:

- a) contacting a compound with cultured neuronal cells [transfected with] expressing a mutated protein or treated with a neurotoxin that induces neuronal cell death; and
- b) determining the number of cultured neuronal cells that die;

wherein a decreased number of dead cultured neuronal cells in the presence of the compound compared to the number of dead cultured neuronal cells in the absence of the compound is indicative of the compound's ability to prevent neuronal cell death [occurring in a mammal susceptible to or having a neurological condition].

12. (Once Amended) The [method] compound of Claim [9] 47, wherein the neurological condition is a neurological disease whereby glutamate or kainic acid mediated excitotoxicity is involved in neuronal cell death.

13. (Once Amended) The [method] compound of Claim [9] 47, wherein the neurological condition is Huntington's disease or Alzheimer's disease.

14. (Thrice Amended) A method for assessing the ability of a [MLK inhibitor] compound to prevent neuronal cell death [occurring in a mammal susceptible to or having a neurological condition], comprising:

- a) contacting a [MLK inhibitor] compound with cultured neuronal cells having activated MLK activity, wherein the activated MLK activity is selected from the group consisting of an enzymatic activity, an ability to bind a SEK1 protein, and an ability to phosphorylate a SEK1 protein;

- b) contacting, in the presence of the compound, surviving cells from step (a) with an agent that induces apoptosis; and

c) comparing the level of apoptosis in the cells in the presence of the [MLK inhibitor] compound with the level of apoptosis in the cells in the absence of the [MLK inhibitor] compound;

wherein the [MLK inhibitor] compound is a potentially useful drug for treating the mammal when the level of apoptosis in the cells in the presence of the [MLK inhibitor] compound is less than the level of apoptosis in the cells in the absence of the [MLK inhibitor] compound.

16. (Once Amended) The method of Claim [14] 15, wherein the neurotoxin is glutamate, quinolinic acid or kainic acid.

17. (Once Amended) The method of Claim 14, wherein step (b) is performed by transfecting the surviving neuronal cells with nucleic acid encoding a mutated form of huntingtin or amyloid precursor protein.

19. (Twice Amended) A method for [screening] assessing a compound's ability to inhibit MLK activity [and thereby prevent neuronal cell death occurring in a mammal susceptible to or having a neurological condition], comprising:

a) contacting a compound with a MLK protein and substrate therefor, wherein the MLK protein is selected from the group consisting of MLK1, MLK2, MLK3, and combinations thereof;

b) measuring the level of MLK activity, wherein the MLK activity is selected from the group consisting of an enzymatic activity, an ability to bind a SEK1 protein, and an ability to phosphorylate a SEK1 protein;

c) comparing the level of MLK activity in the presence of the compound with the level of MLK activity in the absence of the compound, wherein a decrease in MLK activity in the presence of the compound is indicative that the compound has an ability to inhibit MLK activity [is a MLK inhibitor];

d) contacting the compound with cultured neuronal cells having activated MLK activity; and

e) comparing the occurrence of apoptosis in the cells in the presence of the compound with the occurrence of apoptosis in the cells in the absence of the MLK inhibitor; wherein the MLK inhibitor is a potentially useful drug for treating the mammal when the occurrence of apoptosis in the cells in the presence of the MLK inhibitor is less than the occurrence of apoptosis in the cells in the absence of the MLK inhibitor].

21. (Twice Amended) The method of Claim [20] 19, wherein the [MLK] enzymatic activity is kinase activity.

22. (Once Amended) The [method] compound of Claim [19] 51, wherein the neurological condition is a neurological disease whereby glutamate or kainic acid mediated excitotoxicity is involved in neuronal cell death.

23. (Once Amended) The [method] compound of Claim [19] 51, wherein the neurological condition is Huntington's disease or Alzheimer's disease.

24. (Twice Amended) A method for assessing a compound's ability to inhibit MLK activity [and thereby prevent neuronal cell death occurring in a mammal susceptible to or having a neurological condition], comprising:

a) incubating a compound in the presence of a MLK protein and appropriate MLK substrate therefor, under conditions sufficient for enzymatic activity, wherein the MLK protein is selected from the group consisting of MLK1, MLK2, MLK3, and combinations thereof; and

b) determining the presence or amount of phosphorylated product;
wherein a change in amount of phosphorylated product, when compared to incubating MLK with appropriate substrates absent the compound, is indicative of the compound's ability to inhibit the enzymatic activity of MLK [and thereby prevent neuronal cell death in a mammal susceptible to or having a neurological condition].

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29. (Twice Amended) A method for assessing a compound's ability to inhibit MLK kinase activity [and thereby prevent neuronal cell death occurring in a mammal susceptible to or having a neurological condition], comprising:

a) contacting a neuronal cell with a compound under conditions sufficient for MLK enzymatic activity; and

b) determining the presence or amount of phosphorylated MLK product;
wherein a change in amount of phosphorylated product, when compared to incubating a cell absent the compound, is indicative of the compound's ability to inhibit MLK kinase activity [and thereby prevent neuronal cell death occurring in a mammal susceptible to or having a neurological condition].

30. (Twice Amended) The method of Claim 29 further comprising:

c) determining cell viability after step (a);
wherein any increase in the cell's viability status relative to a control is indicative of the compound's ability to inhibit MLK kinase activity and thereby [affecting the viability of the] prevent neuronal cell death.